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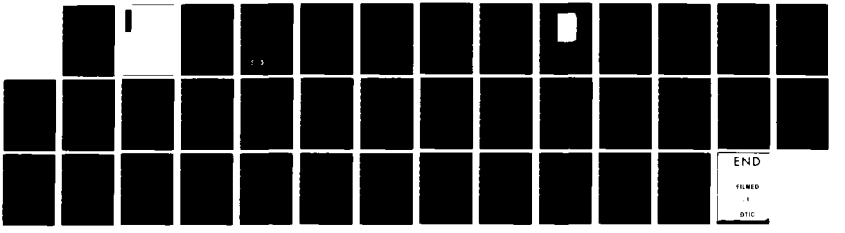

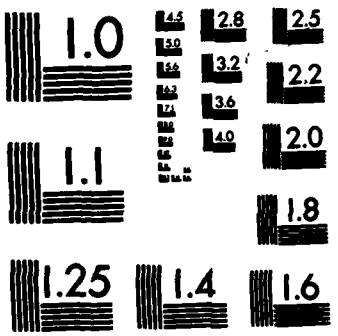

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Our laboratory elected to carefully evaluate these effects utilizing methods and models that lended themselves not only to qualitative observation but to the collection of quantitative data that would stand the rigors of statistical

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FOREWORD

Citations of commercial organizations and trade names in this report do not constitute an official Department of the Army endorsement or approval of the products or services of these organizations.

In conducting the research described in this report, the investigators have adhered to the "Guide for the Care and Use of Laboratory Animals," prepared by the Committee on Care and Use of Laboratory Animals of the Institute of Laboratory Animal Resources, National Research Council (DHEW Publication No. (NIH) 78-23, Revised 1978).

For the protection of human subjects the investigators have adhered to policies of applicable Federal Law 45CFR46.

One of the objective criterion of conduction block anesthesia is to test for the absence of some "reflex" manifested by normal sensory stimulation of the innervated tissues. Our desire to study the feasibility of electric currents as an agent for inducing local dental and oro-facial anathesia has led us to study pain-mediated reflex contraction of neck musculature resulting from electrical stimulation of tooth pulp receptors. The rationale of this approach assumes that electrical stimulation of the tooth pulp induces action potentials in nerves mediating both pain sensations at the perceptual level of nervous activity and reflex contractions of neck musculature. In addition, the approach assumes that an attenuation of the perception of tooth pain, presumably due to a reduction in sensory input from the tooth pulp arriving at relevant centers in the central nervous system (CNS), is reflected by a concomitant decrement in reflex activity.

Based on the above hypothetical framework, we have designed and conducted experiments to quantitatively measure the efficacy of contraction of neck musculature in response to stimulation of individual teeth in dogs. The efficacy of contraction is quantitatively assessed as the stimulation threshold required to induce reflex activity. The latter phenomenon involves a synchronized twitch of the primary musculature responsible for jaw opening and has been commonly referred to as the linguomandibular reflex.

RESULTS

In accordance with provisions outlined in the research contract, we placed an order for an EA stimulator having rather exacting and versatile characteristics. An order to custom build the unit was place with Neurodyne-Dempsey, Inc. of Napa, California. This award followed an exhaustive survey of commercially available equipment which revealed that such units could not meet our rigorous requirements for versatility, precision and safety. The Neurodyne EA stimulator was completed and delivered in late July.

Prior to arrival of the EA stimulator, a series of experiments was conducted to study the characteristics of the linguomandibular reflex as evoked by tooth stimulation. We found in agreement with previous workers that a stable reflex of reproduable parameters could be so elicited and rather precisely quantitated (0.2 volt, or approximately $\pm$ 1-2%) in terms of its threshold appearance. The reflex behavior showed little dependence on the particular tooth stimulated (local sign) or on time, with the exception that the threshold value would suddenly increase by a factor of two or more when the animal had been under the anesthetic for about one and a half hours. The reflex threshold was directly proportional to the depth of anesthesia, varying by 20-30% as anesthetic levels were allowed to swing from deep stage II through the various planes of stage III. The above phenomena were truly reflex in nature and not the result of direct muscle stimulation through the spread of stimulating currents, as they were shown to be reversibly lost following the local infiltration of neck musculature with a neuromuscular blocking agent (succinyl choline).

1970 continued.

Several experiments have recently been completed in which EA currents were administered concurrently with tooth stimulation. The results of one such experiment are described below. These findings are typical of the results of all experiments.

We first sought to test whether EA currents applied to the gingiva would influence linguomandibular reflex amplitude. The experimental procedure was initiated by conducting repeated threshold determinations for digastricus muscle twitch until consistent values were obtained in response to stimulation (1Hz, rectangular pulses, 3msec. pulse duration) of the left maxillary canine. Once repeatable theshold values were verified. Ea current (100Hz, bidirectional pulses, 1% duty cycle) were administered and concurrently a reflex threshold determination was rapidly accomplished. EA current application was then promptly terminated, and several additional threshold determinations were made to check the reversibility of any induced effects. The reflex threshold was markedly reduced when EA currents were administered concurrently with tooth stimulation. The reflex amplitude resulting from suprathreshold stimulation was also significantly augmented by simultaneous gingval stimulation using the EA current source. Analogous results were obtained for the inverse stimulus situation in which EA currents (100Hz, bidirectional pulses, 10% duty cycle) were periodically administered to the tooth during gingival stimulation (1Hz, rectangular pulse, 3 msec. pulse duration); that is tooth and gingival stimulation were again synergistic to reflex contraction of the digastricus muscle.

Similar results were noted in three other experiments. In addition, mutual synergism was also noted between tooth and gingival stimulation when the latter was conducted at 50 Hz and with a 1% duty cycle. Ea current application had no demonstrable effect under the stated experimental conditions when administered at frequencies of 10^3, 10^4 and 10^5 Hz with average currents up to one milliampere and a duty cycle of 10%. Spasms were induced in perinasal musculature at the 1 ma current level apparently as the result of direct muscle or motor nerve stimulation.

Effective investigation of the potentialities of dental electro-anesthesia (EA) presupposes the use of a suitable animal preparation. An excellent site to initiate orofacial pain is found in the tissue which also has optimal relevance, the tooth pulp. The most direct manifestation of such painful activity potentially useful as an index of pain against which to test EA would seem to be pulp-driven contractions of superficial neck musculature; unfortunately, the physiology of this system proved unsatisfactory to the task. The latter results dictated the development of an index of pain in the central nervous system (CNS).

The present report describes the development of such a CNS index of pain, and preliminary experiments testing the effects of EA using the pain model system. The model involves recording ipsilateral cortical evoked responses (ICER) from the sensorimotor cortex of the curarized cat, elicited by stimulation of rimotor cortex of the curarized cat, elicited by stimulation of tooth pulp. These particular cortical responses are believed to be projections of midbrain and thalamic pathways concerned in the conscious perception of pain.

RESULTS

Following many preliminary experiments to isolate and characterize ICER, five protocols in which the effectiveness of EA-train attenuation of ICER have been completed. Fig. 1 indicates the general nature of the data. The central trace group represents recordings obtained immediately following the EA-train, while the upper and lower group represent pre-EA and recovery (1 minute post -EA) episodes, respectively.

In general, the results of all episodes to date can be qualitatively summarized as follows. For a short time following EA train termination (several seconds), ICER is significantly reduced under the proper EA stimulus conditions, and, therefore, ICER is supposedly reduced during EA also. To be effective the interfering stimulus train must be of sufficient intensity (.03-1.0 ma)to be perceived (non-painful) if administered to humans but not so intense (10 ma) as to induce further pain, and must be of frequencies (30-30,000 pps) roughly bounded by the fusion of the pulsatile sensation and by the responsiveness of nerve trunks to electrical stimulation at the low and high ends respectively. The after effects of EA last for as long as 30 seconds, the strength and duration being proportional to the effectiveness of ICER block just following EA termination. It must be emphasized that these are tentative generalizations. The nature of the data, which is acquired without the help of signal averaging, is buried in ongoing biological activity, and many experiments must be completed and the results combined to average out the severe biological variations imposed by such "noise."

It has been shown that the administration of analgesic levels of nitrous oxide cause significant attenuation of cortical responses elicited by painful stimuli. We felt it pertinent to compare EA-induced interference

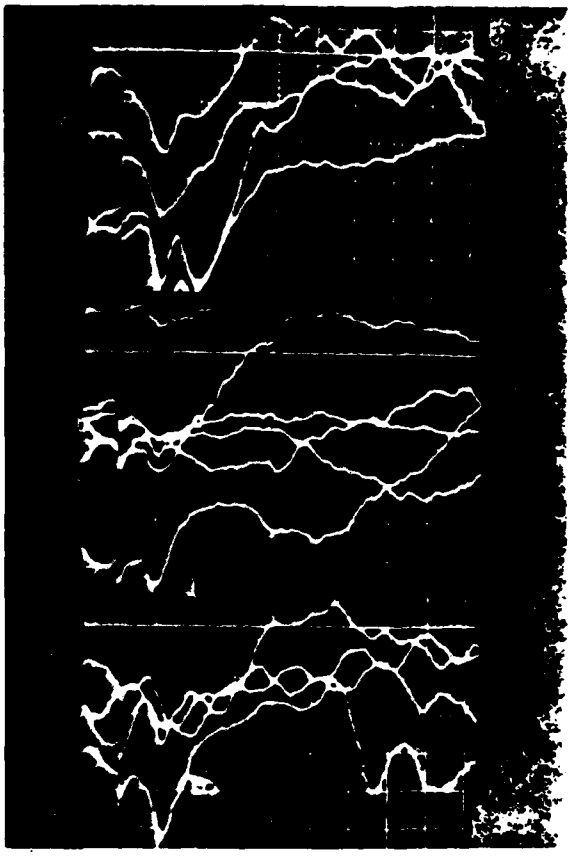

Figure 1. Ipsilateral cortical responses (ICER) from SI elicited by pulp stimulation of maxillary 3rd molar, experiment of 11/4/71. Top 4 traces, recorded 1 second apart, are pre-EA controls. Middle 4 traces were recorded at 1 second intervals during administration of 80% N_2O in O_2, and the lower 4 traces represent recovery 5 minutes later. Note marked attenuation of the first positive peak and later extended negativity in similar fashion to that seen following EA (Figure 1). Calibration: 100 V/div. and 10 msec/div., positive down.

of ICER to that impairment afforded by this analgesic agent. Fig. 1. indicates results typical of the limited number of trails completed to date. The control group of traces represent activity during the administration of 80% N_2O in oxygen, and the groups above and below depict control and recovery traces respectively. It will be noticed that the administration of N_2O alters ICER in a fashion analogous to EA, in that the amplitude of the initial positive peak is significantly reduced in amplutude whereas response latencies remain essentially unchanged. Waveform parameters following the initial positive peak are much more variable for control, EA and N_2O traces, although the prominent negative wave which immediately follows the initial positivity is also attenuated by both N_2O and EA in comparable manners.

It is felt important to demonstrate that the ICER test stimulus current is completely contained within the tooth pulp, in spite of the fact that the use of bipolar pulp stimulation and the location of electrodes make the opportunities for stimulus spread quite remote. In preliminary experiments using the maxillary canine of the cat, it was conclusively demonstrated that current confinement was obtained, as, following removal of the pulp mass and filling the chamber with gutta percha, stimulation with the same currents which evoked ICER activity earlier were no longer effective. Unfortunately, the current-frequency EA characterization experiments used the maxillary 3rd. premolar (necessary to improve ICER efficacy), and the multiroot nature of this tooth precluded complete pulp removal, negating the use of pulp extirpation as a proper control. Therefore, a new control procedure is soon to be instigated, involving tooth extraction, sealing the root canal, reinsertion of the tooth into the socket and finally restimulation, in an attempt to verify that the ICER responses are thereby lost and hence must be solely driven by stimulation of pulp afferents.

Effective preliminary investigation of the potentialities of orofacial electroanalgesia (EA) presupposes the use of a suitable animal preparation. The critical elements in the choice of the preparation include the species, a suitable means to initiate orofacial pain, and the development of some index of this pain to be used in evaluation of the effectiveness of various EA administration protocols.

We elected to use the cat for the experimental animal as the most logical compromise between the considerations of similarity to the human, association with previous neurological literature, and cost. An excellent site to initiate orofacial pain, the tooth pulp, has been thoroughly worked out in this animal, substantiated by demonstrations of the similarity of pulp sensibility in the cat and human. As an index of pain perception, we chose to look at ipsilateral cortical potentials evoked by tooth pulp stimulation, because the cortex is believed to be at least predominantly responsible for perception, the selected activity traverses midbrain structures necessary for pain reaction in the cat, and this is the only pathway with direct cortical input whose transmission is subject to attenuation by the analgesic mixture Nitrous Oxide-Oxygen.

RESULTS

Cortical responses elicited by stimulation of the ipsilateral maxillary carnassial tooth were recorded from the region of Coronal Gyrus. This region corresponds to the overlapping SI-SII facial projection are described for the infraorbital region of the cat. The responses were surface positive, usually of an amplitude near 60 μV, but varying from 40-130 μV, with a rounded peak of latency 10 msec (± 2 msec S.D.) to initiation and 15 msec (± 2 msec S.D.) to apex. Individual cortical responses were apparent to single-sweep observation over an area of 2-4 mm in diameter in the analgesic preparation. Light doses of barbiturates or Halothane caused progressive reductions in cortical response amplitude at a given recording site and in the area of cortical surface from which responses could be observed in single-sweep trials.

Prior stimulation of adjacent gingiva with 10 second trains of bidirectional pulses of the proper waveform parameters resulted in attenuation of ipsilateral pulp-evoked cortical responses, with no significant alteration in response latencies. Amplitudes of individual evoked responses following gingival stimulation of optimal parameters were attenuated 70-80% when compared to individual responses in the absence of gingival conditioning stimulation. Figure 2-A illustrates the general nature of the results. The central trace was recorded one second following termination of a gingival stimulation episode while the traces above and below represent control and recovery conditions respectively. Administration of Nitrous Oxide-Oxygen mixtures above levels which are analgesic in humans and produce lethargic states in cats also result in significant attenuations of pulp-elicited cortical evoked responses (Fig. 2-B) in confirmation of previous work. The response alterations induced by gingival stimulation [illegible] by Nitrous Oxide mixtures are quite analogous when compared [illegible] response criteria.

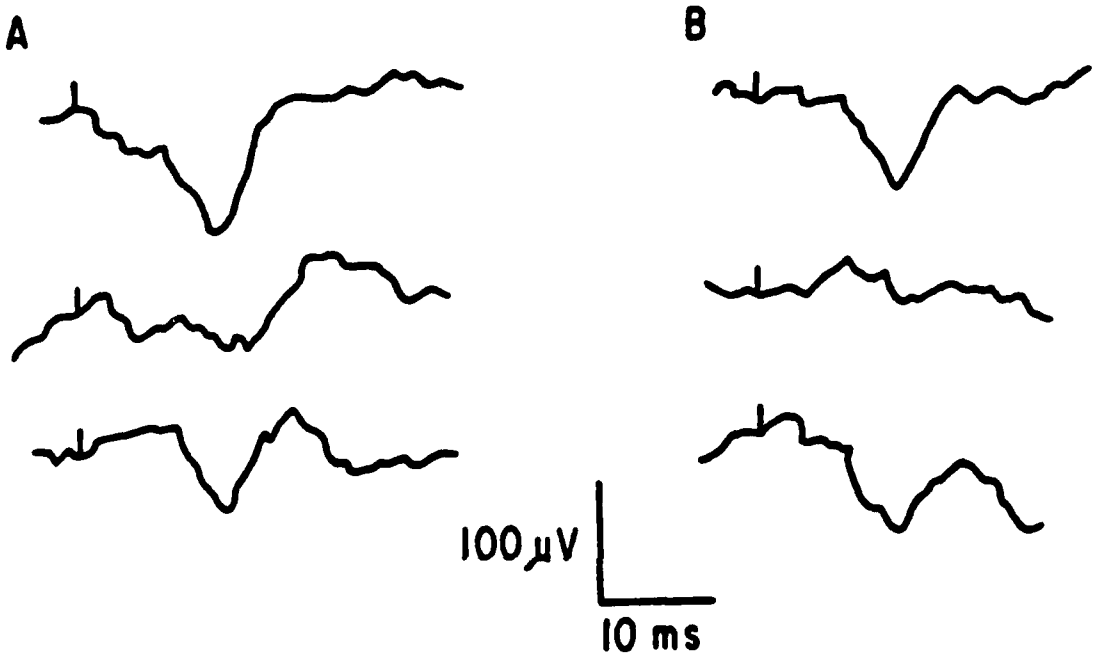

Fig. 2 Individual surface recordings of slow-wave responses recorded on the ipsilateral Coronal Gyrus elicited by stimulation of maxillary carnassial tooth pulp. A. Responses recorded just prior to (upper trace), immediately following (central) and four minutes after (lower) a 10 second gingival stimulation train (1 ma average current, 300 pps, 50% duty cycle). B. Responses recorded just prior to (upper) and 6 minutes following (central) the initiation of Nitrous Oxide-Oxygen (75:25) and 15 minutes after (lower) return to control levels of the analgesic mixture. Calibration values refer to all traces. The responses were selected to convey characteristics deemed significant while being relatively free from ongoing cortical activity.

1972 continued.

An organized survey of certain prominent waveform parameters was carried out in the present experiments. All permutations of average currents of 0.1, 0.3, 1.0, 3.0, and 10.0 milliamperes and of frequencies 30, 100, 300 and 1,000 pulses per second at a fixed duty cycle of 50% were studied and statistically evaluated. There was obviously no significant difference between results for various frequencies of gingival stimulation at a given level of current, as the rank order of values for the four frequency groups at each value of current indicated a complete absence of systematic trends. This may be related to the fact that the duty cycle was constant so power was solely determined by mean current, and to the findings of Hahn that touch thresholds are unrelated to frequencies over the range of 60-1000 pps. For this reason, all values at a particular current were grouped for statistical analysis and are reported as such in Table I. It will be noticed that the value for a current level of 0.1 milliampere does not differ by 1 SEM (standard error of the Mean) from values found in the absence of current, whereas gingival stimulation differs from controls by several SEM units for all other current levels. The optimal effect appears at a current of 3.0 milliamperes in our data but this value is not statistically different from the values for 1.0 and 10.0 milliamperes.

Although many prior studies have shown that pulp stimulation can be accomplished without involvement of gingival and periodontal receptors, a series of experiments was performed to verify that stimulus spread did not occur. In five cats, the pulp of the test tooth was extirpated and it was demonstrated that subsequent restimulation resulted in no responses even at markedly elevated stimulation currents. Secondly, monopolar stimulation of the test tooth using one tooth electrode and one gingival electrode resulted in pulp-like responses at low voltages, while at much higher intensities, short latency, sharp (Lemniscal) responses appear which are analogous to those resulting from bipolar stimulation of gingiva (four cats). This result is consistent with previous results even though Lemniscal activity is considered to be predominantly projected contralaterally because some ipsilateral components from orofacial loci, although small by comparison, have been demonstrated. Lastly, in two cats, pulpectomies were conducted on the homologous maxillary carnassial contralateral to the test tooth, and it was demonstrated that intratooth stimulation at markedly elevated intensities resulted in no detectable responses, while stimulation of nearby gingiva produced Lemniscal responses at low thresholds. Stimulation of the homologous contralateral carnassial with normal pulp produces pulp-like responses, confirming that the responses are bilaterally represented.

An active program is currently being conducted in our laboratory to assess the feasibility of using electrical currents to induce local anesthesia or analgesia. Prior to the present contract term, we demonstrated that presumed innocuous electrical stimulation of gingiva was capable of attenuating inputs to the sensory cortex of cats elicited by stimulation of toothpulp (pain). Based upon these encouraging results, we have designed and initiated a new experimental series in animals to permit the detailed evaluation of the feasibility of three candidate mechanisms deemed as having reasonable potential for use in local electroanalgesia (EA), namely, pain receptor block, nerve conduction block, and gating (intermodality) interactions. Basically, the experiments involve simultaneous EA and test stimulation of tooth pulp in the cat coupled with electrophysiological recording of activity in the sensory trigeminal nuclei of the brainstem. The animal model and experimental equipment array have undergone extensive modification to permit conduct of the definitive experiments, and detailed experiments have been initiated on receptor block mechanisms. In addition, a separate experimental series has been initiated in humans involving tooth stimulation and the effects of the concurrent application of EA to gingiva on verbal reports of perceptual experience. Facilities, personnel, and protocols have been acquired or designed to meet the anticipated new NIH requirements for human investigation. In addition, sophisticated stimulation equipment is now under construction, while preliminary experiments proceed using a clinical vitalometer.

RESULTS

Based upon the results of the monopolar and bipolar 'Dose-Response' curves, the following model has been tentatively formulated. There are three regions within a tooth where nervous tissue may be activated: a) the receptors or terminal nerve branches directly underneath the particular dentinal tubules which communicate directly with the electrode preparation; b) main nerve fibers in the pulp chamber and c) main nerve fibers in the root canal. The initial activity seen with increasing voltage and which plateaus at rather low voltages for both monopolar and bipolar stimulation is probably activation of receptors and nearby terminal nerve branches. With monopolar stimulation at somewhat higher voltages, the increased response amplitude accompanied by short latency responses would appear to be due to activation of additional pulp fibers in the root canal coupled with stimulation of periodontal ligament elements joining the pulpal nerve at the apical foramen, as current density would be expected to be high in these regions using monopolar stimulation. Bipolar stimulation, on the other hand, would not be expected to spread into the root canal and the apical foramen, and in this case such activity is not seen. The increased amplitude of 'pulp' responses without the emergence of short latency 'periodontal' responses seen with much higher voltages using bipolar stimulation is probably the result of the direct stimulation of main nerves in the pulp chamber, while the further increases in 'pulp' activity accompanied by periodontal responses occasionally seen at extremely high stimulus intensities is most likely due to spread of bipolar currents to extrapulpal tissues under these extreme conditions.

1973 continued.

This model must be qualified as being quite tentative, of course, because the data is limited at this time and there are no precedents in the literature. However, the results to date are consistent with this hypothesis and the model will be continually tested with additional experimental protocols. Once this or some other model is verified, it will provide a powerful tool with which to test the effectiveness and mechanisms of the various EA possibilities, as we will be able to precisely define exactly what tissue is being stimulated and where the activation is occurring.

It is premature to speculate on what processes may be involved in the accumulative effects noted during EA anodal d.c. 'Recepter Block'. Possibly it is an artifact of some deterioration of the overall preparation; this possibility is to be tested but is unlikely under the rather tight physiological monitoring and support capabilities to which we routinely subscribe. Alternatively, it may be a real local effect resulting from iontophoresis or secondary upset of intracellular metabolic processes. Experiments are being designed to permit delineation of the mechanisms and ramifications of this phenomenon.

The purpose of the human investigations are to provide the ultimate analytical tool at the level of perception and to provide a situation appropriate for solutions of human engineering and psychological aspects of administration. As the human experimental series is in its infancy, it is most logical to direct the first major experimental protocol to a situation analogous to our previous work in animals, testing the effects of generalized stimulation of adjacent extrapulpal tissue on corticopetal inputs to sensory cortex. This is precisely the experimental protocol which we plan to use in the initial studies, as described under 'Methods'. In general, individual human experimental series will be sequentially matched to analogous neurological protocols to provide optimal conditions for crossover of information.

As mentioned previously, an extremely important factor in the field of pain and its control is the motivational or emotional element as distinct from the pure sensory element of pain perception. This complex problem is being handled in three ways in the current program to circumvent difficulties which have constantly plagued evaluations of pain control. First, Signal Detection Theory protocols and analytical techniques are being employed to permit independent quantification of EA on both the motivational and pure sensory elements. Secondly, protocols are to be included using experimental pain (tooth stimulation) in which anxiety levels are intentionally elevated to mimic more closely the conditions of uncertainty and apprehension experienced with pathological pain. Finally, especially later in the project, a concentrated effort will be conducted using patients experiencing chronic pain in which the true interplay of emotional and pure sensory components are unquestionable. It is believed that this balanced approach, utilizing both neurological versus human studies and experimental versus pathological conditions will provide the ultimate in efficiency in fully characterizing the feasibility of local or regional E.A.

Electrical currents are unquestionably capable of attenuating nerve transmission and perceptual awareness under proper circumstances. Our laboratory is specifically assessing the feasibility of using electrical currents to control acute or chronic orofacial pain. Prior to the present contract term, we domonstrated electrically-induced attenuation of presumed painful inputs to sensory cortex in animals. Subsequently, these encouraging preliminary results were extended by the development of an animal model system to examine in detail three candidate mechanisms of local or regional electroanalgesia (EA) and the concurrent development of a model system to permit the initiation of preliminary human experimentation. The animal work reported for the current year includes completion of the animal model development, a dose-response characterization of the effects of direct current anodal blockade of tooth pulp (pain) afferent activity (block of activity at the sensory receptor, the first candidate mechanism selected for study), and some initial experiments characterizing the nature of retained post-stimulus elevations in pulpal excitability. The human work reported for the current year includes completion of an ultrasafe electronic stimulation facility and experimental array, the development of tooth pulp (pain) and gingival (EA) stimulation protocols and appliances, and the completion of three experimental protocols designed to demonstrate preliminary EA feasibility and to provide data critical to the design of future experimental protocols for the rigorous characterization of EA effectiveness. The present human protocols mimic our prior animal work, and the future efforts will also be designed for maximal interplay between the two programs. Animal experiments must precede human studies for each candidate mechanism studied due to practical and institutional constraints related to human rights and welfare.

RESULTS Animal

The present results indicate that the application of anodal blocking currents at low to moderate levels or even high blocking intensities for short periods of time produce significant alterations in pulp excitability while being quickly reversible upon block cessation. These results are consistent with recent reports which show that d.c. blocks applied to peripheral nerve are capable of blocking various components of the compound action potential and of activity in single fibers and that these effects are reversible within a few seconds following termination of the block. However, intense blocks or moderate blocks for prolonged time periods were not readily reversible, and successive blocks showed accumulative effects since less blocking current was required to generate equivalent response attenuation. The notation of accumulative effects confirms a previous finding involving anodal blockade of the tooth pulp in the awake cat using a reflex index of pulp excitability. Although the nature of the accumulative effects and short-term irreversibility were not revealed by the present or prior work, both phenomena suggest effects on the nervous tissue of the pulp other than simple membrane hyperpolarization, since membrane time constants are expected to be quite short. Nevertheless, these results do not necessarily imply long-term irreversibility since behavioral studies show the day-to-day repeatability of blocking procedures using currents as high as 60 ua. We are therefore continuing the anodal d.c. EA blocking experiments to permit

1974 continued.

Further characterization of post-EA excitability alterations and histological consequences of prolonged EA administration of moderate and high intensities.

The use of field potential recordings in the present study is similar to recordfng nerve compound action potentials in that the responses of a large and distributed population of unit elements is involved. It is known that the disappearance of the compound action potential does not necessarily imply that all activity is blocked, since desynchronization of unit activity would have the same result and in fact has been shown to occur. However, preliminary to such an apparent block changes in latency are apparent, as would be expected in the case of a mere desynchronization of the remaining responsive elements. The present findings are therefore likely to be the result of a true block of afferent conduction rather than mere desynchronization as attested by the lack of changes in latency in the Strength-Response data during or following the administration of anodal blocking currents.

The present results indicate that levels of anodal blocking currents of several tens of microamperes, sufficient to block human perceptual and cat reflex responsiveness, produce a widespread influence of pulp excitability when applied at the occlusal end of the pulp chamber in the cat. Both the pulp excitability and the antidromic recording tests revealed similar alterations in pulpal excitability regardless of whether the blocking electrode or one of the other tooth electrodes was employed for the excitability test. These results rule out an effect of anodal blockade localized to the immediate vicinity of the blocking electrode. Also, the fact that anodal blocking currents resulted in quite large bipolar threshold elevations indicates that the excitability changes were distributed throughout the main pulp chamber, the area through which such bipolar currents are distributed. The use of the monopolar electrode configuration is known to provide only an ambiguous interpretation in terms of localizing the actual point of nervous stimulation, since the site of excitation may include structures in the root canal or in the periapical locations in addition to the pulp chamber proper. The fact that monopolar Strength-Response tests also revealed elevated thresholds but not to the same extent as in bipolar trials suggests that the monopolar test stimulus may have been spreading to structures outside of the pulp chamber whose excitability may also have been affected by the blocking current but not to the same degree as the main pulp chamber. Also, the monopolar Strength-Response results showed that the blocking current had to be applied at the occlusal end of the pulp chamber for widespread effectiveness, in spite of the fact that it seems plausible to expect blocks in the root canal where high current densities are anticipated. This may imply that the blocking currents exert their effects on more vulnerable receptor or terminal nerve fiber regions at the pulp periphery rather than on main nerve fibers in the pulp or root canal. In any case, experiments involving electrical stimulation techniques of the present form cannot be used to define precisely the localization of the block, in spite of a recent claim to the contrary, since it is not possible to distinguish activation of nerve terminals and/or receptors at the pulp periphery from the direct stimulation of main nerve fibers in central areas of the pulp chamber.

1974 continued.

In conclusion, the results show that anodal direct blocking currents ranging to the order of 50 ua results in the reversible attenuation of pulp excitability in a dose-dependent manner. Blocking currents of higher intensities further attenuate pulp excitability, but also result in physiological changes which are not immediately reversible. Delineation of the mechanisms of the latter effects will be tested in further experimentation. These results are summarized in a manuscript recently accepted for publication.

RESULTS Human

Initial periods of the current contract year were involved in design, construction and assembly of the stimulation equipment array and facility and in the establishment of Signal Detection Theory analytical formats. In addition, many preliminary experiments were conducted to aid development of the EA electrode and the test tooth stimulating appliance and to permit preliminary delineation of waveform parameters for initial quantitative characterizations of EA feasibility in humans. The completion of these preliminary tasks permitted conduct of the first quantitative experimental protocol described immediately below (Random Trials Program), the results of which led to two subsequent protocols which are described in turn.

Random Trials Program.

Our initial human experimental program involved the random presentation of each of the five levels of test stimulus intensity. Half of the test presentations were accompanied by the concurrent administration of an EA stimulus train termination. EA stimuli were interjected on a randomized schedule.

Examination of non-EA versus EA trials as to the frequency of occurrence of a reported decrease in perceived intensity (with respect to the sensory category expected for that trial based upon stimulus intensity) indicated no apparent EA effect ($p>0.1$). A decrease in perceived intensity occurred in 43 percent of the trials without EA and 55 percent of the EA trials. However, if the first non-EA trials following each EA trial were considered statistically, a significant decrease in perceived intensity was found 68 percent of the time ($p<0.05$). The mean number of sensory categories by which reports decreased below the expected category for trials in which EA was effective was 1.5, 1.1 and 1.9 for stimulus levels three, four, and five, respectively (levels in which pain was perceived). It was concluded from these results that there was a lag in the effectiveness of the EA following its onset, and, therefore, the Random Trials Program was inappropriate for evaluation of EA effects.

Alternate Episodes Program.

To improve the characterizations in the face of delayed EA effects, a second series of experiments was performed involving multiple test stimulus episodes with or without a continuous train of accompanying EA. Each episode consisted of five test stimulus presentations with each of the five test stimulus intensities represented once in randomized order. Episodes were presented in groups of three, half of the groups involved the "EA / no-EA / EA" presentation pattern and half were patterned "no-EA / EA / no-EA".

1974 continued.

As in the Random Trials Program, examination of individual non-EA versus EA trials as to the frequency of occurrence of a reported decrease in perceived intensity (with respect to the sensory category expected relative to the stimulus intensity) indicated no apparent EA effect ($p>0.1$). A decrease in perceived intensity occurred in 48 percent of the non-EA trials and 53 percent of the EA trials. However, if the first two trials and the last two trials of each episode are considered, a pattern of EA effects emerges. In non-EA episodes, 55 percent of the first two trials but only 38 percent of the last two trials showed a decrease in perceived intensity. In contrast, for EA episodes, 35 percent of the first two trials and 54 percent of the last two trials showed a decrease in perceived intensity. These results were not statistically significant due to small experimental numbers ($p>0.1$), although the trend was definite and consistent from experiment to experiment. The mean number of sensory categories by which reports decreased below the expected category for trials in which EA was effective was 1.0, 1.5, and 1.1 for stimulus levels three, four, and five in the last-two-trials grouping and was 1.5 for each of the comparable stimulus levels in the first-two-trials grouping. The Alternate Episodes Program was terminated because, as with the Random Trials Program the data indicated a substantial lag in the induction of EA effectiveness (late EA trials showed larger decreases in perceived intensity than early EA trials) which we felt was still being inadequately characterized. This conclusion is further substantiated by the fact that the data of the Alternate Episodes Program showed that EA effects spilled over into subsequent non-EA episodes (early non-EA trials showed larger decreases in perceived intensity than late non-EA trials).

Prolonged induction Program.

The Prolonged Induction Program was devised to permit extended periods of time for EA induction. In this program, random trials unaccompanied by EA were initially presented until basal performance had stabilized. EA was then administered continuously during experimental episodes composed of 12-16 presentations of the five test stimuli following a randomized protocol. Two to six complete EA episodes were obtained in various experimental sessions. Within 5 to 10 minutes following completion of EA data collection, additional baseline data was collected to verify that the subject's basal control values had remained stable.

The mean percentage of trials in which a decrease in perceived intensity was observed (with respect to the sensory category expected relative to the stimulus intensity) was 10 percent for the basal condition. In no instance did a subject report any positive perceptual category when a zero stimulus intensity was presented, and an increase in perceived intensity relative to that expected was reported in only one percent of the total trials. In contrast, considering the last EA episode for each experimental session (regardless of the total number accomplished that day), a decrease in perceived intensity was reported in 69 percent of the trials, a value significant at the .001 level of statistical probability. Averaging the results of all intermediate EA episodes (EA episodes being neither first

1974 continued.

nor last) indicated a decrease in perceived intensity of 30 percent ($p > .001$). A similar decrease was seen when all episodes were considered. The number of trials in which changes in perceived intensity were noted at the third, fourth, and fifth levels of stimulus intensity were essentially equally distrubuted (30, 35 and 35 percent of the total number in which changes occured, respectively). The mean number of sensory categories by which reports decreased below the expected category for trials in which EA was effective was 1.3, 1.0, and 0.9 for stimulus levels three, four, and five, respectively. The efficacy of EA as a function of stimulation intensity cannot be clearly assessed based on the latter data.

Peripheral nerve transmission and appropriate perceptual awareness can unquestionably be controlled by electrical currents under the proper circumstances. Our laboratory is specifically assessing the feasibility of using electrical currents to control acute or chronic orofacial pain. In previous work we demonstrated electrically-induced attenuation of presumed painful inputs to sensory cortex in acute animal experiments. Subsequently, these encouraging preliminary demonstrations of feasibility were extended by the development of two programs; first, an animal model system to examine in detail three candidate mechanisms of local or regional Electroanalgesia (EA), and secondly, the concurrent development of a model system to permit the initiation of preliminary human experimentation. In the program involving acute experiments in animals, we have completed a characterization of the effects of anodal direct current blockades of tooth pulp (painful) afferent activity (block of activity at the sensory receptor, the first candidate mechanism selected for study), involving both a dose-response characterization of the efficacy of EA stimulation and the nature of prolonged post-EA hypoexcitability. The latter studies involved field-potential recordings in the trigeminal sensory complex of the brainstem. Subsequently, we have designed our experimental system to permit recording from single neurons in the central nervous system and have developed experimental protocols to permit recording from single pulp-driven units in the Gasserian ganglion. Finally, preliminary acute experiments have been initiated to characterize the effects of intermittent EA currents as opposed to the direct EA currents previously studied. Turning to the human experimental program, we previously developed an ultrasafe electronic stimulation facility and equipment array affording the ultimate in safety to the experimental subjects, and, subsequently, we have developed the requisite techniques for the electrical stimualtion of tooth pulp to initiate experimental pain and the means to apply EA stimulation to areas of the oral mucosa. Once development of the human model system was completed, we conducted three experimental protocols designed to demonstrate preliminary EA feasibility. In the current year, we have conducted an extensive series of baseline studies to verify model validity, and, based upon this data, have completed a preliminary protocol involving modulated EA waveforms which appear to afford greatly increased effectiveness. The present human model system mimics our original feasibility model in the acute animal experiments; in future efforts, it will also be designed for maximal interplay between the animal and human programs. Animal experiments must precede human studies for each candidate mechanism studied due to practical and institutional constraints related to human rights and welfare. We also report on the development of an animal behavioral model, which is nearly operation, and should provide powerful additional flexibility in assessment of EA efficacy and physiological and psychological safety.

RESULTS Animal

Three candidate EA mechanisms are to be investigated in the overall, long-range program. It is most efficient to study one mechanism at a time. We chose to study 'Receptor Block' initially, as it involves the application of both a test stimulus and the EA stimulus to the same structure. The latter configuration permitted much more flexibility in delineating the mechanisms of tooth sensibility, a topic which was relatively poorly

understood at the time and yet which was of crucial importance to our study of all three EA mechanisms, since we needed to understand the detailed nature of the tissue being stimulated for correct interpretation of the subsequent blockage of its neurological innervation. Our choice to conduct the 'Receptor Block' studies initially permitted simultaneous accomplishment of both the quantitative characterization of 'Receptor Block' and the details of pulpal sensibility.

A rigorous characterization of tooth sensibility and other technical details regarding electrical stimulation of the tooth pulp has been completed in our laboratory. These results permitted the definitive specification of criterion necessary to insure the experimental isolation of stimuli to the individual test tooth pulp, criterion substantiated by single-unit data of Greenwood and co-workers, thereby establishing the validity of our experimental model. These criterion have been universally employed in all of our subsequent experiments, involving both trigeminal field-potential recordings and single-unit recordings in the Gasserian ganglion.

Post-EA Effects of Anodal Direct Current Blockade. We have completed the characterization of the results of anodal direct current blockade during the application of EA. During the present year we have completed a characterization of prolonged post-EA hypoexcitability effects. The experimental model used in these studies involved our published brainstem field potential recording model, composed of brainstem field potentials elicited by test stimulation of the tooth pulp as the index of pulpal excitability.

Post-EA definitive experimental protocols were initiated by a systematic exploration of the sensory trigeminal complex of the brainstem in a rostrocaudal and medio-lateral grid of 1 mm steps and at frequent subsurface depths, to permit placement of the electrode for the remainder of the experiment at the point of maximal field potential amplitude elicited by supermaximal stimulation of the test tooth (4 V, 0.1 ms.). A series of threshold determinations were then conducted over a period of 10 minutes to permit the determination of the average pre-block pulpal excitabilities for both the monopolar and bipolar stimulus configurations. In the absence of other stresses to the pulp, these thresholds were shown in 10 experiments to be stable to within ± 0.02 V over periods of two-four hours (nominally less than 10 percent of threshold and 3 percent of single "response maximum" intensities.

The following post-EA experiments were then performed to characterize pulpal excitability during and especially following the administration of EA currents of various intensities and durations. For a given experiment, an EA current of 20, 40, or 60 μa was administered for, successively, 2, 4, 8, 16, and 32 minute episodes, or until long-term hypoexcitability (threshold persistently more than 20 percent above control) unsued. EA episodes were always conducted in the order of increasing duration, to minimize interpretive complications introduced by the accumulative effects of EA block which we have described previously. Thus, any accumulative

effects of prior EA episodes became indistinguishably incorporated into subsequent EA episodes. During an EA application episode, both a monopolar and a bipolar threshold determination was made each minute. This procedure was continued upon cessation of the EA episode, although, after the first 10 post-EA recordings, the rate of change of pulpal excitability has usually decreased substantially, allowing an appropriate extension of the recording intervals. If pulpal thresholds eventually returned to within 10 percent of control, the next episode was initiated immediately, given the condition that the minimal permissible inter-EA interval was 10 minutes.

When a particular level of EA was suddenly imposed and maintained for prolonged time intervals, monopolar pulpal thresholds invariably showed a progressive net increase. Occasionally (in 6 out of 15 experiments), immediately following EA onset, threshold values were found to be slightly depressed, but then showed the usual progressive increase as the EA episode continued.

The temporal progression of pulpal hypoexcitability was fairly irregular, with many plateaus and occasional transient increases of pulpal excitability superimposed on the overall net decrease. In general, the higher the EA current, the greater the irregularity.

Following episodes causing even moderate (up to 50 percent) rises in monopolar threshold, recovery was generally smooth, declining to control values within 10 minutes in the majority of cases. Occasionally, longer intervals were required, and a crude relationship between EA intensity and duration and subsequent duration of post-EA hypoexcitability was apparent. The temporal course of the post-EA hypoexcitability was often irregular, in a fashion analogous to threshold behavior during EA.

The above post-EA monopolar threshold behavior was typical of most 20 μa and of many 40 μa experiments. A strikingly distinct phenomenon eventually appeared, however, in certain experiments, as the EA episodes progressed to longer and longer duration. Often, in the latter case, thresholds suddenly increased to excessively elevated values compared to previous EA episodes. For example, in one 40 μa EA series, during both the 8 and the 16 episodes, the monopolar threshold increased to a maximum of only 20 percent above the initial value. The threshold returned to the moderately elevated value at the onset of the 32 minute series and remained there for the first 5 minutes. In the next 10 minutes the threshold rose smoothly through an additional 160 percent. After such a sudden increase, the thresholds generally remained high and labile, often undergoing sudden increases and decreases.

Following the termination of EA episodes in which such abrupt rises in thresholds occurred, the recovery was markedly prolonged. Generally the threshold would drop to an intermediate value and hold it for up to 6 hours after EA termination (the longest time followed in these experiments). In one experiment, the threshold rose substantially after the 32 minute EA episode was terminated. We have classed these responses separately because they were sudden, excessively large, and markedly prolonged, being quite characteristically distinct from the responses typical of lower EA levels and shorter durations.

We have designated this class of responses "irreversibles" because of their distinctive recovery characteristics. In an attempt to quantify this phenomena, we have arbitrarily defined an "irreversible" recovery as one that remains in excess of 20 percent above control for the first 20 minutes of recovery. The probability of occurrence of an "irreversible" increased with longer EA episodes and with higher EA intensities. Neither this conclusion nor the general character of the data was altered by changing the threshold criterion of "irreversibility" from 20 to 10 or 30 percent.

Bipolar pulpal thresholds showed similar responses to EA imposition. Increases of threshold were generally much greater and more brisk, but the same generalizations about irregularities of the progression of hypoexcitability and similarities of time course of successive EA runs can be applied equally to the bipolar series. The initial hyperexcitability was present in each of the runs, but quickly reverted to a progressively efficacious hypoexcitability in all cases. Maximum increases in threshold ranged to 75 percent for EA presentations in which a decline to control values occurred within 10 minutes of EA termination.

"Irreversibility" occurred slightly more often with bipolar as opposed to monopolar test stimulation. The initial sudden rise in threshold that marked the onset of this phenomenon invariably preceded and was more dramatic than the one evidence by monopolar stimulation. In one experiment, the threshold increased to 100 times the control value during EA imposition, but maximum increases were more often in the range of 100-300 percent. The threshold to bipolar stimulation showed even less tendency to recover to the control values once such a sudden increase had occurred. Following termination of EA, four of the "irreversible" thresholds remained near the value they had reached during the time EA had been imposed, one dropped to an intermediate value, and two initially rose before falling to an elevated plateau.

Single-Unit Recordings in the Gasserian Ganglion. Our data of the previous contract year indicated the need to switch to single-unit recording techniques in the Gasserian ganglion. Preliminary efforts directed to this goal involved system design, the acquisition of appropriate equipment, design of the facility and construction of requisite components, and, once the facility was functional, the concurrent development of the surgical preparation and the conduct of preliminary experiments to bring the single-unit recording techniques to operational status. Following these preliminary tasks we conducted extensive baseline experiments to characterize the general properites of pulp-driven ganglionic units, and, quite recently, preliminary experiments have been initiated to regorously define appropriate protocols for the study of intermittent EA application. The results of the initial characterization of ganglionic units and the preliminary results of intermittent EA protocols are described below.

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All pulp-driven units were found to lie deep within the ganglion, quite near the lower border of ganglionic tissue. No pulp-driven units were found in superficial ganglionic strata. Spontaneous activity of pulp-driven units were found in superficial ganglionic strata. Spontaneous activity of pulp-driven units was essentially absent. It is believed that the reported recordings are from the soma of primary afferents, as opposed to their fiber projections, because of the waveform characteristics, the fact that the recordings could be obtained over extended depth ranges of penetration, and the fact that the recordings could only be obtained from cellular areas within the ganglionic preparation. It was usually not difficult to hold pulp-driven units for prolonged periods of time.

Turning to quantitative physiological characteristics of the ganglionic units, unit thresholds, supposedly inversely proportional to excitability but also dependent upon the relationship of the fiber or its terminal segments to the stimulating electrodes, were found to average 165 μa.

The pulp driven ganglionic units observed to date have exhibited latencies averaging 2.75 ms. with a range of 1.3 to 11.6 ms. and having the indicated statistics. Based upon very approximate estimations of the length of the conduction path, and with due consideration for reduced conduction velocities in the glomerular or side-arm section of the unipolar primary afferent cells, as described by Darian-Smith and co-workers, it appears that all of the observed pulp-driven units are associated with the A-delta class of peripheral fibers. The response amplitude, measured as the maximal deviation from the pre-stimulus or baseline level, was found to average approximately 60μa, as indicated. These results suggest that the pulpal cells have relatively small physical dimensions. Two methods have been used to estimate characteristics of refractoriness for the pulp-driven units. First, test of the maximal frequency of an extended train which the units were capable of following yielded the indicated range of rates, which averaged nearly 300 Hz. Secondly, using paired stimulation, it was found that the minimum average interstimulus intervals to which the units responded faithfully following paired stimulus presentations averaged 1.13 ms.

Following the latter baseline characterizations of pulp-driven ganglionic units, preliminary experiments have been initiated to aid the delineation of specific definitive protocols for the evaluation of intermittent EA waveforms. The data to date was not sufficient in any one such protocol to justify detailed analysis. Nevertheless, the data qualitatively can be summarized to indicate that intermittent EA currents in the clinical range (less than 100 μa) have imposed significant attenuations of pulpal excitability. The only waveform that we have examined as of the present time is pulsating direct current, as we are waiting completion of construction of a sophisticated output generator capable of producing our biphasic (alternating current) waveform. The results to date show that

1975 continued.

various intermittent direct current waveforms definitely produced marked elevations of pulpal threshold. Furthermore, the mechanism may be of two types, a low frequency, large duty cycle phenomenon (possibly due to an anodal block type mechanism), and a second high-frequency-dependent waveform having effects relatively independent of duty cycle (possibly related to fatigue or some other metabolic phenomenon). It must be emphasized that these conclusion are quite tentative at present, due to the limited amount of data. A detailed protocol has just been initiated, described in detail in the recent supplement to the October 1975 renewal application but very few of these experiments have been completed. Nevertheless, the latter procedure seems to be quite productive of definitive data, and will be adopted as the first definitive protocol unless information should arise in the near future to dictate experimental design modifications.

In relation to various experiments, histological preparations of pulps exposed to various EA intensities and durations of exposure were obtained from 15 experiments and compared to the respective homologous contralateral controls which had not been exposed to EA. In some cases, cavities were excavated in the control teeth to mimick the electrode preparations in the test teeth as a control for any morphological alterations induced by this procedure. However, in all cases, tissue prepared from control specimens appeared normal and untraumatized in all respects. In contrast, tissue which had been exposed for prolonged periods to intense levels of EA showed evidence of inflammatory infilitrates and marked dilation of vessels, with proteinaceous coagulum and some vaculization bordering extensive areas under electrode sites, which had been used for EA administration.

Tissue prepared from test specimens which received intermediate (less than 50 μa) or low levels of EA showed respectively less marked morphological alterations.

RESULTS Human

Data in the initial stages of the 1975 contract year included what we felt was an amount of experimental variability which seemed to be becoming progressively accentuated. Detailed analysis, nevertheless, did not reveal whether this problem was due to variables of a technical nature, to deficiencies in the experimental equipment array, or to true peculiarities of a physiological nature. We, therefore, felt it necessary to initiate a rigorous series of experiments designed to very carefully standardize all aspects of the experimental protocol, to permit absolute assurance that our experimental model was valid and that the degree of reliability of our previous characterizations of EA effectiveness was adequate. The ultimate results of this rigorous series of baseline experiments confirmed the validity of the model, and we, therefore, returned to continued definitive experiments regarding various EA variables of interst. One definitive protocol was completed by the end of the contract year, a study of the use of modulated Electroanalgesia waveforms, a protocol of high priority as indicated by preliminary data from our laboratory and the data of Limoge.

1975 continued.

Characterization of Baseline Conditions. The major thrust in the baseline studies was an extremely rigorous characterization of all aspects of the experimental protocol. Our methodology of examination of the tooth in initial subject selection procedures was checked regarding all aspects, as was the technique for obtaining dental impressions and the steps in manufacture of the acrylic appliance for tooth stimulation. We also re-examined all aspects of application of the tooth electrode, the Electro-analgesia electrode, and the respective remote electrodes on the ipsi-lateral neck, including detailed characterizations of the electrical properties of these electrodes on both a day-to-day basis and temporally within a given experiment. Furthermore, we very carefully checked all aspects of the electronic equipment array, including a rigorous characterization of all aspects of electrical leakage currents.

Following the above evaluations, an extensive series of baseline experiments were conducted. The baseline studies were composed of experiments in which a large number of baseline episodes were successively administered, each episode containing 24 individual stimulus trials each separated by 20 second intervals. All baseline studies were conducted in complete absence of EA stimulation. An average experimental session involved 5-7 episodes. The first two episodes were always rejected, because data revealed that they contained excessive amounts of variability due, most probably, to initial subject anxiety of initial daily familiarization with the experimental setup.

The data from 257 total episodes in 23 different subject represents the percentage of individual stimulus trials in which the perceived intensity reported by the subject was less than that expected, based upon the level of stimulus intensity. Each subject was used in 1-5 different experiments. The data indicates that, first, different subjects and, secondly, the same subject on different days, were capable of quite reliably reporting the expected responses based upon stimulus intensity. In no case did error rates exceed 10 percent and were usually found to be much less than the latter value. Signal Dectection Theory analysis of the data showed very little bias as indicated by a false positive rate (reporting a sensory category higher than expected) of occurrence under 1 percent.

Modulated EA waveform Experiments. Our preliminary survey of many potential variables, reported in the report of last year, indicated a potentially great importance of modulated EA waveforms. This conclusion is also strongly reinforced by the data of Limoge, indicating that high frequency components in EA waveforms bear prime importance. These considerations pointed to the need for an early definitive series directed to an investigation of modulated EA waveforms, and the results of such an initial definitive series are reported here. The experimental model was strictly adherent to our standard preparation as defined by the baseline experiments described above, to permit optimal control over other potential EA waveform variables.

Modulation of an electrical waveform meant that one or more of the par-

ticular parameters defining that periodic function are made to vary with time according to some other waveform. In our particular case, we defined a modulated waveform as one in which the amplitude of our standard waveform is made to vary periodically with time. Thus, the modulated waveform never actually reached the experimental subject. Rather, the modulated waveform was merely superimposed at some point in the array of electronic equipment producing the actual EA stimulus output, to alter or modify the amplitude of pulses in the EA stimulus train. The other parameters of the EA train, the bidirectional format of a train of rectangular pulses at a particular frequency and duty cycle, remained unchanged.

Prior to initiation of the definitive modulation experimental series, it was necessary to modify the electronic equipment to permit introduction of the modulation waveform. Subsequently, a series of preliminary experiments were conducted to define the particular parameters of modulation for the definitive experiments. Parameters examined in the preliminary experiments included frequency, waveform and amplitude. Modulation frequencies investigated ranged from 0.1 to 10,000 pps (the present characteristics of our equipment did not permit examination of higher frequencies). Based upon the frequency range examined, a frequency of 1000 pps was selected. The modulation waveform selected was a unidirectional sawtooth wave with a modulation amplitude of approximately one third of the total EA amplitude. The modulated waveform was superimposed throughout the EA train, which, in our basic preparation, is left on continuously once the first EA episode has been initiated.

To date, we have completed the collection and analysis on 91 episodes in 19 experiments, involving the use of 9 different subjects. The data indicates several findings of importance. All subjects examined have reported reduced values in stimulus intensity, approaching 100 percent effectiveness upon the application of EA current for extended induction periods. An EA trial is considered effective if the subject reports a lower sensory category than that expected based upon the magnitude of stimulus intensity. Rates of induction varied from subject to subject and from session to session in the same subject. Once the effectiveness of EA current had become manifest, the rate of induction proceded upon a predictable and fairly linear curve. Furthermore, the rates of induction differed substantially between modulated and unmodulated waveforms. The latter factor was also true regarding EA efficacy. Unmodulated current consistently produced a level of 100 percent effectiveness more rapidly than did modulated EA current . However, the degree of this effectiveness was consistently higher using modulated EA current. Furthermore, after modulated EA current had resulted in an effectiveness exceeding approximately 90 percent, a continual increase of efficacy was seen in the form of larger induced changes in the number of sensory categories. That is to say, a pre-established intensity level 5 was more often reported as a 3 or as a 1 than when the calculated effectiveness was less than 90 percent. This was found to be true for both modulated and unmodulated EA current. However, the magnitude of change was consistently greater in the case of the use of modulated EA current.

1976-1977

Peripheral nerve transmission and perceptual awareness associated with pain can be controlled by the application of electrical current. Our goal is to assess the feasibility of using electrical currents (Electro-analgesia, or EA) to control acute or chronic orofacial pain.

Our present work concerns two specific and entirely distinct pain control mechanisms. One mechanism, Gating Block EA, involves a distributed low current-density electrical stimulation of the skin or mucous membranes, and is believed to be effective by virtue of intermodality interactions in the central nervous system, to interference with peripheral nerve conduction, or, more probably, to a combination of both mechanisms. The second pain control mechanism under investigation is Receptor Block EA. The latter technique features localized, low-power electrical stimulation, and is believed to be effective by virtue of interference with receptor mechanisms at the level of actual sensory transduction and/or the block of conduction in initial portions of primary afferents. To reiterate, our work is directed to the study of two totally distinct EA mechanisms, and, realistically, should be viewed as two entirely separate projects.

The Gating Block EA program presently involves two experimental series, Human Psychophysiological Experiments and Chronic (Behavioral) Psychophysiological Experiments, respectively. The Human Experiments of the present contract year were directed first to the study of the efficacy of EA in relation to electrode configurations and anatomical sites of stimulation, and, secondly, to a comparison of the best configuration and site thereby identified with our standard intraoral site used historically. The latter tests were particularly important since the optimal site identified had an extraoral location and therefore offered important advantages regarding accessibility. The Chronic experimental model has been under development for some time. Its principle importance follows from the ability to test analgesia at the perceptual level and the greater flexibility afforded by animal models permitting tests not allowed in humans. During the present contract year, development of the Chronic model was completed and data was collected to quantitatively define its characteristics. In addition, preliminary data derived from the initial definitive EA experiments are described.

The Receptor Block EA program has exclusively involved Acute Neurophysiological Experiments to date. Work of the present contract year first established the feasibility and potential advantages of using a pulsating direct current waveform instead of continuous direct current. This represented a major breakthrough, because we have previously shown that continuous direct current, while effective, induces significant irreversible effects. The pulsating direct current waveforms permitted circumvention of these problems. The latter experiments were followed first with an experimental series to identify the optimal duty cycle of the pulsating direct current waveform, and, secondly, with an experimental series just recently completed to identify the optimal frequency of the pulsating direct current waveform. Investigations of alternating current EA are to be initiated shortly and may provide further waveform improvements.

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RESULTS Human

The Human Gating Block experiments of the present contract year were composed of two phases. Phase I experiments systematically surveyed the use of electrode arrays and the use of various anatomical sites of stimulation. The Phase II effort was composed of a quantitative comparison of the two best stimulus locations identified in Phase I, being the Oral Mucosa near the test tooth and the dermis overlying the ipsilateral Mental Foramen, respectively.

The electrode array studies focused on two sites of EA application, the Mental Foramen and Oral Mucosa, the sites also employed in Phase II. The Mental Foramen experiments were actually conducted late in the contract year after trends of the Phase II experiemnts had become apparent. An electrode "array" consisted of a $6mm^2$ electrode in the standard position for the particular stimulation site, an identical electrode placed distally (medially) with a 6mm separation, and an identical electrode placed proxmally (laterally) with a 6mm separation. EA was applied to the central electrode alone, the central and the distal electrode simultaneously, and the central and the proximal electrode simultaneously. Our equipment was incapable of driving all three electrodes simultaneously. The results indicate that the use of electrode arrays did not result in improved EA efficacy. The experimental numbers are small for each condition studied, as the results obviously indicated no dramatic effect of electrode arrays, and further studies were deemed of low priority and unworthy of further pursuit. The data did reveal one important fact. The distal-standard electrode combination produced results comparable to the use of the standard electrode alone. Based on the latter information, additional tests using a single electrode but shifted 6mm medial to the Mental Foramen indicated results comparable to the standard electrode position ($p > .10$). Therefore, with the Mental Foramen site, there appears to be some flexibility in the position of the single electrode. Regarding the concept of arrays in general, the lack of improved effectiveness coupled with the technical problems associated with multiple electrodes has led to a cessation of their consideration and use.

Results of the Phase I anatomical sites survey involved four active electrode sites in various ipsilateral and contralateral combinations of active and indifferent electrode positions. Four orofacial sites were selected as candidates for EA evaluation based on their proximity to the site of initiation of the experimental pain, to anatomical structures deemed likely to provide current access to deep tissues, or to locations near major sensory nerve trunks. The sites chosen for study were respectively, the buccal Oral Mucosa near the test tooth, an Intraoral Salivary Foramen, and cutaneous locations over the Infraorbital and Mental Foramina. The two most effective sites were found to be the ipsilateral Mental Foramen and the Oral Mucosa near the test tooth. During EA, reported intensities were reduced in 66% and 56% of the trials compared to values expected in the absence of EA for the Oral Mucosa and Mental Foramen stimulus locations, respectively, results which demonstrated a significant EA effect ($p < .01$). The effectiveness found in these tests was less than that of the Phase II effort because fewer sessions were included in each

experiment (the overall induction time was shorter).

Results of the Phase II comparison of the Oral Mucosa and Mental Foramen EA stimulation sites are summarized. The data has been analyzed to show the percent of trials which indicated an EA-dependent alteration of perceived intensity, relative to that expected based on the magnitude of test stimulation. As in all human protocols, each EA session during an individual experiment consisted of 12 EA test trials (and two control trials in the absence of EA). The values shown for each session indicate the total number of the 12 trials which exhibited an EA effect, an EA effect being defined as a subject reporting a higher sensory category than that expected based upon test stimulus intensity. Inspection of the data reveals that EA applied to both the Oral Mucosa and the Mental Foramen resulted in significant EA effects, although during induction, the effectiveness of the Mental Foramen site lagged behind that of the Oral Mucosa. Statistical analysis of the results indicated that the Mental Foramen site did not differ in effectiveness when compared to the Oral Mucosa EA stimulus location following comparable induction times ($p > .10$), a significant finding in view of the greatly increased accessibility of the former placement. The latter comparison was based on the session 4 data, as session 5 data was not available for the Mental Foramen site.

The Phase II data can also be subjected to a second analysis based on the magnitude of the sensory category shift observed during each effective EA trial. This analysis was discussed in our recent Contract Renewal Application, the results being quantified as the average number of sensory categories involved in EA-dependent shifts of reported perceived intensities relative to the sensory categories expected based on the magnitude of test stimulation. The results indicated that following full induction, the Mental Foramen site resulted in superior EA as compared to the Oral Mucosa location. An observed average change of 2.0 and 1.5 sensory categories was observed for the Mental Foramen and Oral Mucosal sites, respectively, values which differed statistically ($p < .01$).

RESULTS Animal - Chronic

The conditioning and training of cats to escape or avoid noxious stimuli by pressing a lever is a valuable technique for the study of motivation and behavior and to investigate various anesthetic or analgesic strategies. Typically, a procedure required for training animals to perform a specific response (operant) is referred to as shaping, and involves the prolonged and systematic reinforcement of behaviors (by an experimenter directly interacting with the animal) which at first may be dissimilar to the desired operant, but may be required to orient the subject animal toward the lever or toward a particular area in the experimental environment. Successive minor behavioral modifications are then introduced by the experimenter which more and more approximate the desired response. Finally, the actual operant itself is presented. This procedure is tedious and time consuming, since as many as 15 hours can be required with each animal for successive approximation training or "shaping" to, for example,

1976-1977 continued.

escape aversive stimuli by pressing a lever.

An automatic and much abbreviated method for escape and avoidance conditioning, which circumvents the problems inherent in the basic shaping procedure, is also available. Termed Automatic Shaping, this procedure eliminated the rigorous successive approximation format and significantly reduces the time necessary for conditioning. The experimental environment is rigorously structured such that the probability of eliciting the desired response from the animal is maximized. For example, if the interior dimensions of the response chamber and the location and site of the response lever are correctly determined, then within the first few stimulus trials, the animals exaggerated motor activity in response to, e.g., footshock will lead to contact with the lever and termination of the shock. Following a brief number of trials, the desired operant is often performed with regularity. Furthermore, and very importantly, this system can be automated.

The marked effectiveness of a retangular pulse stimulus train of such a long duty cycle as the 31.6% waveform presently under investigation is difficult to explain. The latter waveform was chosen for examination because a similar effect had been noticed in preliminary studies using experimental pain in humans. In the first approximation, one would not expect the generation of much nervous activity using such a long pulse duration except at the leading and trailing edges of individual pulses. If the long duty cycle waveform proves to be far superior upon completion of the experiments, this waveform will be identified as optimal barring significant side-effects. However, if the other waveforms provide equivalent efficacy at comparable power levels, stimulus formats using shorter pulse durations will be selected as optimal due to concommitant reductions in iontophoresis associated with each EA stimulus pulse.

In addition to marked effectiveness during EA, the data indicates dramatic post-EA effects for all duty cycles. Similar post-stimulation analgesia has been noted in association with TNS investigations in general somatic (non-orofacial) anatomical fields, and was also a characteristic feature noted in our prior human studies using experimental orofacial pain. Neurological mechanisms subserving this phenomenon are unidentified, but since the present studies involved EA stimulation in a dermatome (Trigeminal III) distinct from the origin of pain (Trigeminal II), the effects are almost certainly dependent on interactions in the central nervous system. The observed post-EA analgesia could have profound clinical significance if sufficient efficacy can be obtained, as pre-operative or "waiting room" analgesia may prove to be feasible.

Significant attrition has occurred in conducting animals through the several stages of surgery and training to finally permit collection of Threshold Titration data with accompanying EA. Also, the Threshold Titration data showed a significant amount of variability, as the animals

exhibited a wide range of responses around the mean tolerance level within the control, EA, and post-EA periods. Nevertheless, the data indicate that, given a sufficient number of stimulus trials within each experiment, the experimental model is quite adequate to provide a quantitative measure of average tolerance levels and changes therein induced by the application of EA. The Chronic Psychophysiological model is presently fully operational and on-line, and will provide a powerful tool for the development of EA techniques and the production of safety documentation.

RESULTS Animal-Acute

The present results establish the feasibility of pulsating direct current EA. The optimal waveform based on the data to date is composed of a train of monophasic anodal rectangular pulses of 10% duty cycle and frequency of 1000 pps. At comparable peak intensities (and therefore only 10% of the electrical power), the latter waveform produced blockades of pulpal afferent activity statistically indistinguishable from continuous direct current EA. Reductions in duty cycle below 10% or the use of frequencies above or below 1000 pps produced a pronounced roll-off in EA efficacy.

Data from the duty cycle series indicated an absence of a main effect for intensity in the statistical analysis of the data ranging from 70-100 μA, indicating the presence of a plateau effect in this range for all duty cycles investigated. A strong tendency toward the plateau effect was also noted in the preliminary series and also in the frequency series if the data of two units is omitted. Perusal of the raw data from individual experiments indicates that most units tend to show a definite plateauing effect in the range of 70-100 μA, but the results are less conclusive in some of the averaged data due to the pronounced effect of a small number of units exhibiting wildly aberrant behavior. The nature of the aberrant behavior is a sudden and seemingly irreversible enormous increase in threshold such that the units cannot be activated at all, apparently the result of exceeding the 'irreversibility threshold' which we have previously described. It appears that the plateau phenomenon is real, but its presence in the average data is obscured by occasional interference of the 'irreversibility' phenomenon. The data is presently being reanalyzed to properly distinguish conclusions following appropriate consideration of both the 'plateau' and 'irreversibility' phenomena.

Results in the Receptor Block program to data are profoundly significant clinically. The data indicates that the use of a continuous train of rectangular anodal pulses (a pulsating direct current waveform) of 10% duty cycle and 1000 pps frequency permits retention of analgesia while affording an order of magnitude reduction in power and negligible irreversibility contingencies, when compared to continuous direct current EA. Experiments scheduled for the immediate future will test the efficacy of alternating current waveforms, desirous because of decreased iontophoresis, and to verify Receptor Block EA at the preceptual level in Chronic experiments.

Our Laboratory effort in dental electroanalgesia began with a literature review in which we argued that even the seemingly low direct currents of tens or hundreds of microamperes result in enormous current densities (current per unit cross-sectional area) of up to 1 ampere/cm^2 when corrected for the restricted cross-section of the dentin available for ionic electrical conductance. These considerations led to a preliminary study in cats on the pulpal excitability effects of monopolar anodal direct currents. It was found that such currents ranging to only 100 microamperes cause a significant dose-dependent attenuation of pulpal excitability, levels which produce analgesia in humans and block reflex responses in animals. Similar results were reported by another laboratory. Furthermore, monopolar direct EA currents ranging to 100 microamperes cause irreversible effects in direct proportion to the magnitude and duration of EA, greatly jeopardizing their clinical applicability. As an alternative to the undersirable direct current EA, we have subsequently studied the efficacy of trains of rectangular pulses on attenuating pulp-elicited activity in single units of the Gasserian ganglion (the proposed work of Phase I was a continuation of this experimental model). First, preliminary study was conducted to quickly survey critical waveform parameters (intensity, duty cycle, frequency) to delineate parametric ranges for more detailed characterizations. The parametric ranges chosen for further investigation were 0-100 microamperes intensity, 1-10 percent duty cycle, and 100-1,000 pps frequency. In addition, information from the literature directed us to extend the upper frequency limit of interest to 100,000 pps to consider both (monophasic) pulsating direct current (PDC) and a (biphasic) pulse train with successive pulses alternating in polarity (AC). First, a duty cycle study using 1000 pps PDC permitted identification of the 10 percent duty cycle as optimal and additionally indicated that maximal pulpal EA efficacy equivalent to continuous DC EA was achieved at an intensity of 70 microamperes. Secondly, a frequency study using 10 percent duty cycle PDC demonstrated that the 1000 pps frequency produced the optimal afferent blockade, equivalent to continuous DC EA. Finally, experiments have been completed in which both PDC and AC Waveforms of intensities ranging to 1,000 microamperes (to cover the majority of intensities employed clinically), were compared to continuous DC EA. The AC waveform produced afferent blockades indistinguishable from continuous DC EA and yet, in contrast to the latter waveform, was nearly devoid of post-EA manifestations of irreversibility. Phase I of the work completed the last step of the overall series of acute pulpal excitability experiments in animals, the identification of induction and recovery procedures commensurate with the previously characterized waveform parameters for maintenance analgesia.

RESULTS

Phase II of the research was completed during the contract year utilizing subjects with acute and chronic oro-facial pain including trigeminal neuralgia, chronic sinusitis, migraine, pain resulting from cervical dislocation.

Each subject was evaluated utilizing the McGill Pain Assessment Questionnaire. Upon selection for the study, each subject was entered into a series of five experimental sessions wherein analgesic current (standard waveform and frequency) was applied at a subsensation threshold level bilaterally over the

1978-1979 continued.

mental foramina. Current was applied for one hour, utilizing two platinum electrodes, 1 cm^2, with physiological gel at the skin-electrode interface.

Each subject was required to complete a McGill Pain Questionnaire prior to the experimental session, after thirty minutes of current administration and at the end of the session. As additional questionnaire was sent home with each subject with instructions for its completion approximately four hours after current administration.

Data from fifty-six (one hundred-three subjects were evaluated under this protocol, forty-seven did not complete five sessions for sundry reasons) subjects are currently evaluated by the methods of Melzack and Torgerson, and Melzack.

Evaluation of the data has shown that, 1) forty-one of fifty-six subjects expressed relief from their particular pain after the completion of a single experimental session. 2) thirty-one of fifty-six subjects expressed relief from their pain in all sessions escept those in which current was not effectively administered (placebo control session). 3) No subject expressed relief from their pain during a placebo-control sessions. 4) One of the fifty-six subjects did not express relief from pain until the fifth experimental session was completed. 5) Twenty-one of one hundred-three were unable to complete the five-session requirement because they remained pain free after one or two sessions.

Clinical Pain Relief Series.

The utilization of EA current for pain control was evaluated in subjects with acute or chronic clinical pain of pulpal origin in the dental clinic. The subjects were recruited from the dental clinic at this institution and were comprised of volunteers who were afflicted with deep carious lesions, fractured teeth, deteriorating restorations, or any other conditions in which the origin of pain could be clearly attributed to afferent activity arising from receptive terminals in tooth pulp alone. Pre-treatment documentation includes a clinical description of the condition of the tooth in question including its location in the dental arch, radiographs when available, and detailed descriptions of the proposed dental treatment. The nature of the pain being experienced by the subject was evaluated by a modified version of the McGill Pain Questionnaire, adapted to the specific dental pain situation.

The rating report was accomplished by the subject pointing to a nearby board with the numberical and verbal scale boldly lettered; the observer recorded responses. After the first report of "no pain" or "Maybe pain" following induction, and at every interval thereafter that the rating fails to fall below "no pain", the lesion/fracture will be probed with a dental explorer. Upon indication of continued analgesia, the proposed treatment was initiated.

The control experiment, in which the entire procedure was to be done with the EA current supply turned off, offered some problems in design. Ideally, the pain model would be uniform across subjects and a double blind treatment of a control group and experimental group would be conducted. The alternative was to perform a control and experimental procedure on each subject, in random order. This alternative would be influenced by any residual effect of the experimental procedure. We chose the second alternative, two consecutive procedures done on each subject in random order with a 30-minute interval between them. Residual effects were to be tested for by comparison of pre-EA and post-EA controls at each reporting interval across all trials. Non-parametric statistics was to be used to test for within procedure effect of the EA current vs. zero current controls at the 5 levels of the rating scale. In addition, subjective descriptions were to be sought in terms of response to the modified McGill Pain Questionnaire and any other subjective impressions at the end of each procedure (control or experimental). Anecdotal, subjective material was to be examined for consistency (or lack thereof) with statistical findings and was to be used, in early stages of experimentation, as a guide in possible modification of the experimental protocol (within guidelines approved by the Committee on Human Research).

RESULTS

The primary effort was devoted to the solution of logistical problems including subject reimbursement, and of technical problems of electrode placement and the familiarization of residents and graduate students with the protocol.

Phase III consisted of two distinct approaches to the control of pain associated with clinical dentistry.

1979-1980 continued.

The first effort utilized so-called Regional analgesia utilizing extraoral electrodes.

Forty-six patients were recruited for this portion of the study. The patients required treatments ranging from root planing and curettage to sharp surgical dissection.

Twenty-two of the forty-six subjects demonstrated an increase in threshold to stimulation after a thirty minute induction period but upon initiation of the dental treatment all patients requested support by standard analgesic compounds. This initial failure resulted in difficulty recruiting patients and in a marked reduction in support by the clinical departments.

An additional nine patients were evaluated under this protocol increasing the current to a level that was perceptable to that patient and the results were unchanged.

The second approach to the control of pain associated with clinical dentistry was in utilization of the so-called receptor block by the direct application of electro analgesic current to those tissues that were to be invaded. These studies are not completed at this writing.

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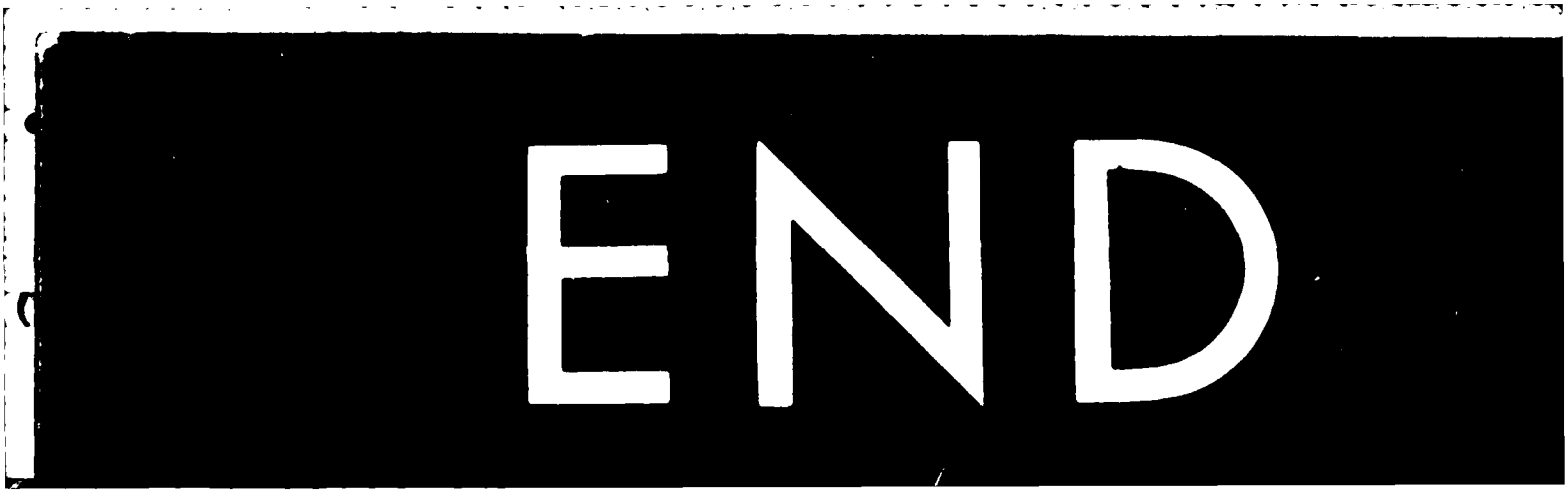
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